The opinion in support of the decision being entered today is not binding precedent of the Board.

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Paper [redacted]

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge Carol A. Spiegel)

ALICE M. WANG, MICHAEL E. DOYLE
and DAVID F. MARK

Junior Party,
U.S. Patent 5,219,727
U.S. Patent 5,476,774

v.

GEORGE J. MURAKAWA, R. BRUCE WALLACE,
JOHN A. ZAIA and JOHN J. ROSSI

Senior Party,
Application 07/402,450

Patent Interference No. 105,055

Before: SCHAFER, TORCZON and SPIEGEL, Administrative Patent Judges.

SPIEGEL, Administrative Patent Judge.

MEMORANDUM OPINION and ORDER
(Decision on Wang preliminary motion 1)

Before us for consideration is Wang's preliminary motion 1 pursuant to 37 CFR § 1.633(a) that all the involved Murakawa claims, i.e., claims 34-35, 38-39 and 42-47, are unpatentable under 35 U.S.C. § 135(b)(1). We grant Wang's motion and remand the case to the APJ for further proceedings not inconsistent with this opinion.

I. Introduction

This interference concerns a PCR[1]-based method for determining the amount of a target nucleic acid sequence in a sample by simultaneously amplifying the target nucleic acid sequence and a known amount of an added internal standard nucleic acid sequence ("control sequence"[2]) with the same oligonucleotide primer pair in a single

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[1] PCR or "polymerase chain reaction" is an in vitro method for enzymatically synthesizing or "amplifying" a target nucleic acid (DNA) sequence. The reagents typically required for PCR include (a) a DNA polymerase, (b) each of the four nucleotide building blocks of DNA (i.e., dNTPs A, T, G and C), (c) a source of template DNA, such as double-stranded DNA containing the target sequence, and (d) two primers designed to be complementary to the bases at the 3' ends of the target DNA sequence.

Amplification of the target sequence occurs in repeated cycles of three defined steps called denaturation, annealing and primer extension. A reaction solution is prepared by adding (c) an excess of primer, (b) all four nucleotides (A, T, G and C) and (a) a DNA polymerase to (c) a source of template DNA, e.g., double-stranded DNA. In the first step, the double-stranded DNA is heated near boiling to separate the paired strands of DNA into single strands. In the second step, the temperature is lowered to allow the primers to anneal or hybridize to their complementary DNA sequences on the single strands produced in the previous step (because of the large excess of primers, the two separated DNA strands will bind to the primers instead of to each other). In the third step, the DNA polymerase produces complementary copies of the initial single strands of DNA from the primers hybridized to the DNA. That is, primer annealing produces a nucleic acid molecule that is partially double-stranded where the primer has hybridized and partially single-stranded where the primer has not hybridized. The DNA polymerase uses the double-stranded annealed primer portion as a substrate and sequentially adds a nucleotide to the 3' end of the primer which is complementary to the nucleotide which is "across" from it on the single-stranded portion of the nucleic acid molecule to produce a "primer extension product."

The three steps are repeated. The original and newly synthesized double-stranded DNA are separated. In this way the double-stranded products of the previous cycle become new templates for the next cycle such that at each cycle the amount of the target sequence flanked by the primers essentially doubles. Assuming a 100% efficiency at each cycle, one copy of a target sequence in a sample would be increased to about a million copies after 20 cycles.

[2] In this decision, the terms "standard," "reference" and "control" are equivalent when used in reference to the added internal standard nucleic acid. Furthermore, the term "predetermined quantity" is equivalent to the term "predetermined amount" in this decision.

reaction mixture (Count 1). This interference also concerns a plasmid[3] having a 5' sequence and a 3' sequence which provide upstream and downstream primer hybridization sites that are identical to the 3' and 5' primer hybridization sites on a target DNA (Count 2), such that the plasmid is useful as a control sequence.

II. Findings of fact (FF)

The following findings of fact are supported by a preponderance of the evidence.

1. The junior party is ALICE M. WANG, MICHAEL D. DOYLE and DAVID F. MARK (**Wang**).

2. Wang is involved in the interference on the basis of two patents:

   (i) U.S. Patent 5,219,727 ("the Wang 1993 patent"), which issued June 15, 1993, based on application 07/413,623, filed September 28, 1989, and

   (ii) U.S. Patent 5,476,774 ("the Wang 1995 patent"), which issued December 19, 1995, based on application 08/028,464, filed March 9, 1993.

3. Claims 1-4 and 6-10 of the Wang 1993 patent correspond to Count 1 in this interference.

4. Claims 5-7, 10-12 and 15-18 of the Wang 1995 patent correspond to Count 1 in this interference. Claims 1-3 and 8-9 of the Wang 1995 patent correspond to Count 2 in this interference.

5. The senior party is GEORGE J. MURAKAWA, R. BRUCE WALLACE, JOHN A. ZAIA and JOHN J. ROSSI (**Murakawa**).

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[3] A plasmid is a small, circular, self-replicating DNA molecule found in bacteria.

6. Murakawa is involved in the interference on the basis of application 07/402,450 ("Murakawa '450"), filed September 1, 1989.

7. Murakawa '450 has been accorded benefit for the purpose of priority of

(i) application 07/143,045 ("Murakawa '045"), filed January 12, 1988, and

(ii) application 07/148,959 ("Murakawa '959"), filed January 27, 1988.

8. Claims 34-35, 38-39 and 42-47 of Murakawa '450 correspond to Count 1 in this interference. Claim 45 of Murakawa '450 corresponds to Count 2 in this interference.

9. Pursuant to 37 CFR § 1.607, Murakawa requested an interference with the 1995 Wang patent (Ex. 2023).

10. According to Murakawa,

> The patent which claims subject matter which interferes with subject matter claimed in the present application is U.S. patent no. 5,476,774 (the "'774 patent") issued on December 19, 1995 to Wang et al. ... . The '774 patent was issued from Ser. No. 028,464, filed March 9, 1993, which purports on its face to be a continuation of Ser. No. 413,623, filed September 28, 1989 (now U.S. patent no. 5,219,727), ... [Id., p. 4.]
>
> * * * * * *
>
> The '774 patent issued on December 19, 1995, which is less than one year prior to the filing of the present claims/request. Therefore, the provisions of 35 U.S.C. 135(b) have been satisfied. [Id., p. 7.]

Other findings of fact follow below.

III. The legal standard

Section 135(b)(1) of 35 U.S.C. states that "[a] claim which is the same as, or for the same or substantially the same subject matter as, a claim of an issued patent may not be made in any application unless such a claim is made prior to one year from the date on which the patent was granted." To establish entitlement to the earlier effective

date of existing claims for purposes of the one-year bar of 35 U.S.C. § 135(b), a party must show that the later filed claim does not differ from an earlier claim in any "material limitation." Corbett v. Chisholm, 568 F.2d 759, 765-66, 196 USPQ 337, 343 (CCPA 1977). "Inclusion of a limitation in a claim to avoid the prior art provides strong evidence of the materiality of the included limitation. Parks v. Fine, 773 F.2d 1577, 1579, 227 USPQ 432, 434 (Fed. Cir. 1985)." In re Berger, 279 F.3d 975, 982, 61 USPQ2d 1523, 1527 (Fed. Cir. 2002). "If all material limitations of the copied claims are present in, or necessarily result from, the limitations of the prior claims, then the copied claim is entitled to the earlier effective date of those prior claims for purposes of satisfying 35 U.S.C. § 135(b)." Id., 279 F.3d at 982, 61 USPQ2d at 1527.

IV. The Wang 1993 patent claims contain two material limitations -- (1) use of predetermined initial amount of a control sequence and (2) use of a shared primer pair for amplifying the control and target sequences

11. In an Office action mailed October 21, 1991 (Ex. 2015, pp. 3[4] and 5), claims 1-27 of the application that matured into the Wang 1993 patent were rejected under 35 U.S.C. § 103 as unpatentable over Chelly et al., "Transcription of the dystrophin gene in human muscle and non-muscle tissues," Nature, 333:858-860 (June 30, 1988) (Ex. 2009).

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[4] According to the Examiner,

> Chelly et al. teach a method of quantitating a target nucleic acid using co-amplification of the target and an internal standard nucleic acid. The Chelly et al. teaching differs ... in ... using a gene different from the target as the standard; this gene binds primers which are different from those bound by the target. [Ex. 2015, p. 3, pentultimate ¶.]

12. Wang argued that

> ...Chelly fails to disclose two critical elements ... . The first missing element is the use of a single pair of primers to amplify both target and standard polynucleotides. ... the second missing element is a known concentration of a standard. ... Without knowledge of the original quantity of standard present, there is no way of using PCR to quantify the amount of target polynucleotide in a sample. [Ex. 2016, para. bridging pp. 4-5.]

13. The next Office action, mailed May 6, 1992, maintained the rejection of kit claims 17-19 of the application that matured into the Wang 1993 patent over Chelly et al. (Ex. 2017, pp. 4-5).

14. In response, Wang amended claim 17[5] and argued that

> ... Chelly is missing two elements of the present invention. First, Chelly does not provide that a single pair of primers can amplify both a segment of the standard and a segment of the target sequence. ... Second,... . Chelly did not provide a known quantity of standard. [Ex. 2018, para. bridging pp. 21-22.]
>
> * * * * * * *
>
> ...Chelly does not provide an internal standard nucleic acid and primers able to amplify <u>both a segment of the internal standard nucleic acid and a segment of the target</u>. therefore, Chelly does not provide the elements of the kit of claim 17 and those claims dependent thereon ... . [<u>Id</u>., p. 24, para. 2, original emphasis.]

15. The final Office action, mailed October 30, 1992, withdrew the rejection of the claims over Chelly (Ex. 2019).

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[5] A marked up copy of amended claim 17 reads as follows (brackets indicated deletions; underlining indicates additions):

> 17. (Amended) A kit for the quantitation of a [particular] target nucleic acid segment in a biological sample comprising individual containers which provide:
>
> <u>a predetermined initial amount of</u> an internal standard <u>nucleic acid segment for quantitation of a target nucleic acid</u>; and
>
> [at least one] <u>an</u> oligonucleotide primer pair wherein said primer pair can serve to amplify a nucleic acid segment contained within the internal standard <u>together with a segment contained within the particular target nucleic acid</u>. [Ex. 2018, pp. 3-4.]

16. In the Notice of Allowability, mailed January 8, 1993, the Examiner's Statement of Reasons for Allowance stated that "[t]he closest prior art (Chelly et al) uses, as a standard, a nucleic acid that binds a different set of primers than the target and therefore teaches away from use of a standard which will bind the same primers as the target" (Ex. 2020, p. 2, last para.).

17. The Wang 1993 patent issued on June 15, 1993 with one independent and nine dependent method claims. Independent claim 1 reads (emphasis added):

> A method for quantifying a target nucleic acid segment in a sample, which method comprises the steps of:
>
> (a) **adding** to said sample **a predetermined initial amount of standard nucleic acid segment wherein said standard nucleic acid segment binds to same primers as are bound by said target nucleic acid segment** in a reaction mixture;
>
> (b) treating said sample under conditions suitable for carrying out a polymerase chain reaction, wherein said nucleic acids are rendered single-stranded and exposed to an agent for polymerization, deoxynucleoside 5'-triphosphates, and a pair of oligonucleotide primers, wherein **said pair of primers is specific for both the target and standard nucleic acid segments**, such that an extension product of each primer of said pair can be synthesized using separate strands of the target and standard segments as a template for synthesis, such that the extension product of one primer, when it is separated from the template strand, can serve as a template for the synthesis of the extension product of the other primer of said pair wherein said amplified target and standard segments are distinguishable by size or by the use of internal probes, wherein said internal probes may be differentially labeled for each of said amplified target and standard segments;
>
> (c) separating the primer extension product from the templates on which they were synthesized to form single-stranded molecules;
>
> (d) repeating steps (b) and (c) on the single stranded molecules produced in step (c) at least one, whereby each repeat of steps (b) and (c) is one amplification cycle;
>
> (e) measuring the amounts of the amplified target and standard segments produced in step (d); and
>
> (f) calculating from the amplified target and standard segments produced in step (d) the amount of said target nucleic acid segment present in the sample before amplification.

Wang contends that the claims of the Wang 1993 patent contain three material limitations -- (1) the use of predetermined initial amount of a control sequence, (2) the use of a shared primer pair for amplifying the target and control sequences, and (3) the placement of the control sequence on a plasmid (Paper 26, pp. 8-10, 14 and 19). Murakawa maintains that the earlier Murakawa claims contain the asserted material limitations (1) and (2), and that (3) is not a material limitation (Paper 35, p. 1).

We agree with Murakawa that the placement of the control sequence on a plasmid is not a material limitation of the Wang 1993 claims for three reasons. First, Wang has not pointed to, and we do not find, any rejections, including prior art rejections, during the prosecution of either the Wang 1993 or 1995 patents which were overcome by amending the claims with a "plasmid" limitation. Second, Henry A. Erlich, Ph.D., Wang's own expert witness, admits that it is not a critical limitation, i.e., having a shared primer pair amplify the target and control sequences is critical, not limiting the control sequence to a plasmid (Ex. 1010, p. 31, l. 10 - p. 33, l. 18).[6] Third, in its reply

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[6] Dr. Erlich testified upon cross-examination as follows (Ex. 1010, p. 31, l. 10 - p. 33, l. 18):

Q: ... The fact that there's a plasmid claimed is not a material limitation, is it?
A: I don't think so. The material limitation referred to in [paragraph] 16 [of Dr. Erlich's Declaration, Ex. 2011] is the shared primer pair.
Q: OK. So the fact that it's -- it's a shared primer pair, that's important. And the fact that the shared primer pair will also amplify a plasmid isn't critical; is that correct?
A: The crucial element is having the shared primer pair amplified the reference sequence as well as the target sequence. That's the crucial element.
Q: It's not crucial that the reference be on a plasmid. It could be in any form, correct?
A: I think that's correct.

* * * * * *

Q: OK. But either generating the reference either way work be it a plasmid or synthetically, correct?
A: In principle, they should be both able to work as a control or reference or standard sequence.

(Paper 34, pp. 4-5), Wang recharacterized the issue as "whether any of the Murakawa claims (i.e., those filed or pending prior to the § 135(b) critical date) necessarily resulted in those two material limitations", i.e., a predetermined initial amount of a reference nucleic acid, and the use of a shared primer pair.

V. The earlier Murakawa claims

In determining the level of ordinary skill in the art, we considered several factors, including the educational level of the inventors, the sophistication of the technology, the educational level of active workers in the art and the content of the prior art of record. In our opinion, Henry A. Erlich, Ph.D.[7] and Gerald F. Joyce, M.D., Ph.D.,[8] are persons of ordinary skill in the art.

18. The critical date for purposes of 35 U.S.C. § 135(b)(1) is June 15, 1994, one year after the issue date of the 1993 Wang patent.

A. Earlier Murakawa claims recite use of predetermined initial amount of a control sequence

19. Involved Murakawa independent reaction mixture claims 34, 35, 46 and 47 and kit claim 44 all recite having "a predetermined initial amount of a control sequence" (Ex. 2010). Murakawa claims 34, 35 and 44 were initially presented on December 18, 1996

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[7] Dr. Erlich testified for Wang that, in his opinion, "a person of ordinary skill in the art of PCR in 1988 and '89 was a person with a Ph.D. degree or equivalent experience in genetics, molecular biology, or similar technology and at least two years of laboratory experience with PCR" (Ex. 2011, ¶ 5).

[8] Gerald F. Joyce, M.D., Ph.D., testified for Murakawa that, in his opinion, "a person of ordinary skill in the art of PCR in 1988 and 1989 was person with an undergraduate degree in the life sciences or chemistry, a graduate degree in molecular biology, biochemistry or a closely related discipline, and at least one year of post-doctoral experience. If the person's graduate degree was not in molecular biology or biochemistry, his or her graduate school course work and laboratory experience would have included significant contributions from these sciences. The person would have had one to two years experience with PCR." [Ex .1004, ¶ 5.]

(Ex 2023) and subsequently amended. Murakawa claims 46 and 47 were initially presented on December 19, 1996 (Ex 2029) and subsequently amended. None of the involved Murakawa claims had been presented or were pending as of June 15, 1994, the critical date.

20. Wang and Murakawa both agree that (i) Murakawa '959 claims 15-17 and 20 (Ex. 2027,[9] p. 3; Ex. 2028,[10] p. 2) and (ii)(a) Murakawa '450 claims 26-28 and 30, as originally filed September 1, 1989 (Ex. 2006) and (ii)(b) claims 31-33, added on December 4, 1991 (Ex. 2007), use a predetermined quantity of a control sequence. [See Murakawa admission in Paper 35, p. 3 of Wang's statement of material fact 20 in Paper 26, p. 8.]

Use of a predetermined initial amount of a control sequence is explicitly recited in (i) Murakawa '959 claim 15 (and claims 16,17 and 20, dependent thereon, (Ex. 2027, p. 3; Ex. 2028, p. 2)) and (ii)(a) Murakawa '450 original claim 26 (and claims 27-28 and 30, dependent thereon (Ex. 2006)) and (ii)(b) claim 31 (and claims 32 and 33, dependent thereon, added on December 4, 1991 (Ex. 2007)).

21. Murakawa '959 claim 15 reads (Ex. 2027, pp. 1-3, emphasis added):

> A process as defined in claim 7
>
> [A process for minimizing false negative data in the identification of a target viral RNA sequence in a peripheral blood or H-9 cell sample which comprises
> (i) selecting said target viral RNA sequence;
> (ii) simultaneously subjecting (a) said sample and (b)

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[9] Murakawa "Amendment" filed February 27, 1989 in Murakawa '959.

[10] Murakawa "Amendment Responsive to Final Action Mailed July 3, 1989" filed July 25, 1989 in Murakawa '959.

at least one reference nucleotide sequence which does not include said target sequence or which contains substantially more nucleotides than said target sequence;
to polymerase chain reaction amplification under conditions appropriate to simultaneously amplify said target sequence if present in said sample and said reference sequence;

(iii) denaturing the amplification products produced by step (ii);

(iv) subjecting the denatured amplification products of step (iii) to hybridization conditions separately and sequentially with oligonucleotide probes homologous to said target sequence and to said reference sequence;

whereby hybridization of the probe with the amplified reference sequence provides a positive control and minimizes the possibility of false negative data]

wherein a predetermined quantity of the reference sequence is utilized in step (ii)(b); the probes utilized in step (iv) are labelled; and, the presence or absence of the reference sequence in the denatured amplification products of step (iii) is detected in step (iv) by southern blot hybridization with said labelled oligonucleotide probes.

22. Murakawa '450 original claim 26 read (Ex. 2006, p. 21, emphasis added):

A process as defined in claim 18

[A process for minimizing false negative data in the identification of a target viral RNA sequence in a peripheral blood cell sample which comprises:

(i) selecting said target viral RNA sample;

(ii) simultaneously subjecting (a) said sample and (b) at least one synthetic RNA sequence which does not include said target sequence or which includes substantially more nucleotides than said target sequence to polymerase chain reaction amplification under conditions appropriate to simultaneously amplify said target sequence if present in said sample and said reference sample;

(iii) denaturing the amplification products produced by step (ii);

(iv) subjecting said denatured amplification products of step (iii) to hybridization conditions separately and sequentially with probes homologous to said target sequence and to said reference sequence,

each of said probes being removed from a sequence

with which it hybridized prior to the separate and sequential separation of said amplification products to hybridization with another of said probes;

(v) determining whether said amplified target and reference sequences hybridized with said probes homologous therewith]

wherein a predetermined quantity of the reference sequence is utilized in step (ii)(b); the probes utilized in step (iv) are labelled; and, the presence or absence of the target sequence and the presence of the reference sequence in the denatured amplification products of step (iii) is detected in step (iv) by Southern blot hybridization with said labelled oligonucleotide probes.

23. Murakawa '450 claim 30, as of December 1, 1991, read (Ex. 2007, pp. 1-2):

A process as defined by claim 18

[A process for discerning false negative data or false positive data in the identification of a target viral RNA sequence in a peripheral blood cell sample which comprises:

(i) selecting said target viral RNA sequence;

(ii) simultaneously subjecting (a) said sample and (b) at least one synthetic RNA reference sample which does not include said target sequence or which includes substantially more nucleotides than said target sequence or which includes at least about 20 nucleotides less than said target sequence to polymerase chain reaction amplification under conditions appropriate to simultaneously amplify said target sequence if present in said sample and said reference sequence;

(iii) denaturing the amplification product or products produced by step (ii);

(iv) subjecting said denatured amplification product or products of step (iii) to hybridization conditions separately and sequentially with probes homologous to said target sequence and to said reference sequence,

each of said probes being removed from a sequence with which it is hybridized prior to the separate and sequential subjection of said amplification products to hybridization with another of said probes;

(v) determining whether said amplified target and reference sequences are hybridized with said probes homologous therewith, false negative data being indicated

> by failure of said probes to hybridize either to the sample or to the reference sequence and false positive data being indicated by hybridization of the target sequence probe and by the absence of hybridization of the reference sequence probe]
>
> **wherein a predetermined quantity of said reference sequence is used in step (ii)(b)** and the probes utilized in step (iv) are labelled.

B. Earlier Murakawa claims do not require or necessarily result in use of a shared primer pair for amplifying control and target sequences

24. Involved Murakawa independent reaction mixture claims 34, 35, 46 and 47 and kit claim 44 all require an oligonucleotide primer pair which can serve to amplify said control sequence and said target nucleic acid (i.e., viral RNA) sequence (Ex. 2010).

25. According to Dr. Erlich,

> ...use of a primer pair is conventional in PCR. That is, in order for PCR to proceed, the reaction requires a primer at each end of the two ends of the sequence to be amplified. It is important to distinguish between the use of different pairs of primers for the control sequence and the target sequence such as taught by Chelly *et al.* (Exhibit 2009) from the use of a shared primer pair for both the control and target sequences. None of the earlier Murakawa claims[11] recite the inclusion or use of a shared primer pair. Moreover, such a shared primer pair does not necessarily arise from the limitations of those earlier Murakawa claims. That is, for example, the subject matter of the earlier Murakawa claims all can be practiced using primer pairs that are not shared between the control sequence and the target sequence. [Ex. 2011, ¶ 12.]

Murakawa disagrees, alleging that Wang's recitation of "a standard nucleic acid segment that 'binds to [the] same primers' as are bound by the target nucleic acid segment" is the same as Murakawa's reference "to amplifying a reference sequence

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[11] The "earlier" Murakawa claims refer to filed or pending by June 15, 1994, i.e., claims 1-33 as they existed as of June 15, 1994 (Exs. 2006-2008) and to the claims of the earlier Murakawa applications (Exs. 2004-2008, 2021-2022 and 2024-2028) (Ex. 2011, ¶ 6).

and a target sequence simultaneously by PCR" when Murakawa's claims are construed by one skilled in the art in light of the Murakawa specifications (Paper 35, pp. 16-17). Specifically, Murakawa argues that Murakawa '450 original claim 18, by virtue of reciting a Markush group expressly including a sequence which includes substantially more nucleotides than the target sequence, necessarily results in the use of a "shared primer pair" (Paper 35, pp. 21-22). Murakawa further argues that Murakawa '450 original claim 30 "when properly construed, requires a known amount of an identifiable reference sequence that binds the same primer pair as the target sequence, and further requires that the reference sequence be amplified by PCR in the presence of (and therefore simultaneously with) the target sequence" (id., p. 22)

Thus, to prevail, Murakawa must show that the earlier Murakawa claims not only require a predetermined initial amount of a control sequence, but also require or necessarily result in the use of a shared primer pair.[12]

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[12] On cross-examination, Dr. Joyce testified as follows:

Q: As a part of preparing your declaration did you try to find a single claim within the Murakawa applications that's directed exclusively to the combination of the two material limitations in the Wang claims for quantitation?
A: Did I try to? I would say, no, I didn't try to. But I would have noticed the extent to which a claim pertained to the so-called material limitations in the case.
Q: Did you find a single claim that was directed exclusively to the combination of the two material limitations in connection with quantitation?
A: No, I did not.
[Ex. 2030, p. 19, l. 25 - p. 20, l. 12.]

* * * * * *

Q: So as you sit here today you're not aware of any claim that's directed exclusively to quantitation containing those two material limitations in the Murakawa cases?
A: Any single claim?
Q: Yes.
A: Correct.
Q: So what you've done as part of coming up with with [sic] your opinion is to combine various claims together to come up with what you believe contains those two material limitations?
A: Yes.

26. Murakawa '450 original claim 18 reads (Ex. 2006, p. 19, emphasis added),

> A process for minimizing false negative data in the identification of a target viral RNA sequence in a peripheral blood cell sample which comprises:
>
> (i) selecting said target viral RNA sequence;
>
> (ii) simultaneously subjecting
>
> (a) said sample and
>
> (b) **at least one synthetic RNA sequence** which does not include said target sequence or **which includes substantially more nucleotides than said target sequence**
>
> to polymerase chain reaction amplification under conditions appropriate to simultaneously amplify said target sequence if present in said sample and said reference sequence[13];
>
> (iii) denaturing the amplification products produced by step (ii);
>
> (iv) subjecting said denatured amplification products of step (iii) to hybridization conditions separately and sequentially with probes homologous to said target sequence and to said reference sequence,
>
> each of said probes being removed from a sequence with which it hybridized prior to the separate and sequential subjection of said amplification products to hybridization with another of said probes;
>
> (v) determining whether said amplified target and reference sequences hybridized with said probes homologous therewith.

27. Murakawa '450 original claim 19 reads (Ex. 2006, p. 20, emphasis added),

> A process as defined by claim 18 in which the reference sequence utilized in step (ii) is
>
> (i) a sequence present in the T-cell receptor expressed by cells affected by the virus containing said viral RNA;
>
> (ii) a preselected RNA sequence present in substantially all of the cells of said sample;
>
> (iii) **a sequence including said target and constructed by a multi-base insertion into a site in said viral RNA preselected with respect to said target sequence**;
>
> (iv) a beta actin sequence.

[Id., p.20, l. 25 - p. 21, l. 11.]

[13] Murakawa '450 original claim 18 lacks antecedent basis for "said reference sequence." For purposes of this discussion we interpret the --at least one synthetic RNA sequence-- as "said reference sequence."

28. Murakawa '450 original claim 30 has been reproduced above (FF 22) and recites, in relevant part,

> (ii) simultaneously subjecting (a) said sample and (b) **at least one synthetic RNA reference sample** which does not include said target sequence or **which includes substantially more nucleotides than said target sequence or which includes at least about 20 nucleotides less than said target sequence** to polymerase chain reaction amplification under conditions appropriate to simultaneously amplify said target sequence if present in said sample and said reference sequence.

In other words, the issue is whether simultaneously subjecting a sample and any of three possible control sequences, i.e.,

(1) "at least one synthetic RNA sequence ... which includes substantially more nucleotides than said target sequence" (Murakawa '450 original claim 18),

(2) "a sequence including said target and constructed by a multi-base insertion into a site in said viral RNA preselected with respect to said target sequence" (Murakawa '450 original claim 19), or

(3) "at least one synthetic RNA reference sample ... which includes substantially more nucleotides than said target sequence or which includes at least 20 nucleotides less than said target sequence" (Murakawa '450 original claim 30),

to PCR amplification under conditions appropriate to simultaneously amplify a target sequence, if present, and the control sequence necessarily results in or requires use of shared primer pairs.

1. claims 18, 19 and 30 do not exclude use of shared primer pairs

29. Obviously, as Dr. Joyce testified for Murakawa, "[i]f the reference sequence and the target sequence have the same primer binding sites, both the target sequence and the reference sequence will be amplified simultaneously by PCR when the same primer pair, i.e., the shared primer pair, is used" (Ex. 1004, ¶ 34).

However, as noted by Wang in its reply (Paper 34, p. 6), Dr. Joyce merely states what would happen under such conditions, not that simultaneous amplification of the target and reference sequences require use of a shared primer pair.

30. For example, Dr. Joyce also testified that "[i]t is possible to fall within ... claim [18] and not use shared primer pairs" (Ex. 2030, p. 23, ll. 1-5).

2. claims 18, 19 and 30 do not require or necessarily result in use of shared primer pairs

Here, the exact nature and sequence of the three aforementioned possible control sequences are not stated in Murakawa '450 claims 18, 19 and 30. Rather, they are described as (i) having "substantially more" nucleotides than the target sequence or (ii) including "a multi-base insertion" at a "preselected" site in the target sequence or (iii) having "at least 20 nucleotides less" than the target sequence. Neither the size of the target sequence (claim 18) nor the size of the insert (claim 19) is specified.

Pending claims are given the broadest reasonable interpretation consistent with applicant's specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). Furthermore, while claims are read in light of the specification, specification limitations are not read into the claims. Id., 893 F.2d at 320-21, 13 USPQ2d at 1322.

a. "substantially more," "multi-base insertion" and "preselected" site are not terms of art

31. Here, Drs. Joyce and Erlich both agree that, in this context, the terms "substantially more", "multi-base insertion" and a site "preselected" with respect to said target sequence do not have ordinary and customary meanings to one skilled in the art. [Ex. 1004, ¶¶ 24-25; Ex. 1010, p. 23, ll. 8-25, p. 24, l. 24 - p. 25, l. 4.]

i. a control sequence that contains "substantially more" nucleotides than the target sequence, but does not contain the target sequence, cannot use a shared a primer pair

Claim 18 does not require its control sequence to include the target sequence.

32. Indeed, Dr. Joyce testified that claim 18 encompasses a control sequence that contains "substantially more" nucleotides than a target sequence, but does not contain any of the target sequence (Ex. 2030, p. 24, l. 25 - p. 25, l. 4). For this species, a shared primer pair is not only not required, but cannot be used (id., p. 26, ll. 6-10).

As noted by Wang in its reply (Paper 34, p. 2), "it is possible that other reference sequences described in the '450 specification (*e.g.*, T cell receptor surface sequence or ß-actin sequence) are longer and thus have 'substantially more nucleotides' than a target sequence (*e.g.*, where the target viral sequence is the fragment amplified by HIVA and HIVB)."

ii. a control sequence comprising a "multi-base insertion" does not require an insertion "preselected" to preserve the primer binding sites of the target sequence and, therefore, does not require or necessarily result in use of a shared primer pair

33. According to the Murakawa '450 specification,

> [a]n additional aid to quantitation of virus levels in patient samples is provided by **a reference RNA which can be amplified and detected by the same oligonucleotides used for authentic virus RNA samples**.
>
> Such a reference RNA may be a "minigene" or a "maxigene" formed by a multi-base pair insert into or deletion of at least about 20 nucleotides from a unique site. For example **a preferred reference RNA** includes a 21 base pair insert into the KpnI site of the HIV-1 3' ORF (nef) region of the pGEM92 clone described in Example I. An insert of sequence: ... is appropriate.
>
> The transcription product of this clone is 21 bases longer than the

> authentic HIV-sequence but **still hybridizes to with the 25-mer probe HIVC**. It is therefore distinguishable by size from the authentic viral product.
>
> Such "minigenes" and "maxigenes" not only provide an internal control but also an additional aid to quantitation. Because the quantity of "maxigene" [sic, or] minigene RNA originally included in the amplification reaction is known, the amount of signal obtained from the maxi or minigene amplification product can be related to the signal obtained from the patient sample. Hence, the relative quantitation of the original amount of authentic HIV-1 in the patient sample is provided. [Ex. 2006, p. 6, l. 15 - p. 7, l. 8, emphasis added.]

According to Murakawa, this is the only description in its '450 specification of a control sequence containing "substantially more" nucleotides than the target sequence, i.e., a "maxigene" (Paper 35, p. 19). Further according to Murakawa, since the maxigene "can be amplified and detected by the same oligonucleotides used for the authentic virus RNA samples" and the described site of the example is located between the primer binding sites of the viral RNA and the insertion of the multi-base insert does not destroy the primer binding sites of the control sequence, "a person of skill in the art would have interpreted the 'preselected site' in claim 19 to mean a site selected so as not to disrupt primer binding sites" (id., pp. 21-22). [See also Ex. 1004, ¶ 31, where Dr. Joyce voiced the same opinion.]

First, as noted by Wang in its opposition (Paper 35, p. 9), the term "preselection" never appears in the Murakawa '450 specification. Second, as noted above, the term "preselected" in this context does not have an art-recognized meaning. Third, while a "preferred" RNA control sequence might contain an insertion site that does not disrupt

primer binding sites in the base (i.e., target) sequence,[14] "it is generally impermissible to limit claim terms to a preferred embodiment or inferences drawn from the description of a preferred embodiment". Bell Atlantic Network Services v. Covad Communications, 262 F.3d 1258, 1273, 59 USPQ2d 1865, 1874 (Fed. Cir. 2001). Thus, as to claim 19, the dispositive question is whether "a reference RNA which can be amplified and detected by the same oligonucleotides used for authentic virus RNA samples" necessarily requires or results in use of a shared primer pair.

34. Dr. Erlich testified that he considered this language "ambiguous" and that he'd "be more likely to interpret oligonucleotides as referring to hybridization probe rather than a primer pair" (Ex 1010, p. 25, l. 25 - p. 28, l. 5).[15]

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[14] Dr. Erlich testified that even if the insert was at a site between two primers, either a shared primer pair or two different primer pairs could be used for amplification (Ex 1010, p. 28, l. 7 - p. 29, l. 3).

[15] On cross-examination, Dr. Erlich testified:

Q: OK. There's reference to the reference RNA, which can be amplified and decked [sic, detected] by the similar oligonucleotides used for authentic virus RNA samples. Do you see that?
A: Yes.
Q: And that's a definition of RNA or a description of a shared primer pair as you've discussed it in your declaration, isn't it?
A: No, I don't think it is.
Q: Why not?
A: For one thing, the language is ambiguous. Nucleotides, the same nucleotides could be interpreted either as the same oligonucleotides probes or conceivably as a shared primer pair. But as it reads here, it's ambiguous.
Q: But under one interpretation, it can mean a shared primer pair?
A: As I said, it's ambiguous. And actually the way I would read it, given that the products are distinguishable by size, is that when it says "detected by the same oligonucleotides," I think it's more likely to be a probe than a primer pair.
Q: Well, it says, "Amplified and detected by the same oligonucleotides."
A: Yeah. I think in common usage, if you were referring to a, primary you would say amplified by the same nucleotides. And if you meant hybridization, you would say detected by the same nucleotides.
Q: But it could also be interpreted to mean that they both can be amplified by the same primers and detected by the same oligonucleotides; is that correct?
A: Well, as I said, it's ambiguous, and it doesn't specify that. There's an additional reason why I thought it was more likely that this phrase detected by the same oligonucleotides

35. During cross-examination (Ex 2030, p. 54, ll. 3-12), Dr. Joyce testified that

> Q: ... So isn't it true that what unique site could be is that it's to make sure that the probe isn't affected rather than that the primer isn't affected, the primers aren't affected?
>
> A: Yeah. That's just, that's not my reading of these detailed descriptions. My reading is it's primer A, primer B, and probe C, all three of which are the same for both the target sequence and the reference sequence. And I drew my Exhibit A that way.

36. That being said, Murakawa '450 Example I describes amplification of an HIV-1 target sequence HIVA and HIVB oligodeoxyribonucleotide (i.e., primer A and primer B) with subsequent hybridization to oligodeoxyribonucleotide probe HIVC (i.e., probe C) (Ex. 2006, pp. 8-9). Example VI is said to be "Example I ... repeated with the exception that the primer pair beta actin A and beta actin B is included in the amplification reaction mixture" (id., p. 12). Example VII is said to be "Example 1 ... repeated with the exception that **the maxigene primer is included in the reaction mixture**" (id., emphasis added).

Thus, Example VII aids in clarifying the ambiguity noted by Dr. Erlich insofar as it provides a basis in Murakawa '450 for construing "preselecting" an insertion site in a control sequence with respect to a target sequence as meaning that the site should be chosen to avoid disrupting probe hybridization. In other words, there is no explicit

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referred to hybridization probes, as there's other language. And I think exhibit perhaps 2005 or -- yeah, I guess it's the previous exhibit, where the language was similar.

It said detected, amplified and detected by the same oligonucleotides. But it referred to a different primer pair.

So if I were to interpret this phrase, using the language of the 2005 exhibit, I'd be more likely to interpret oligonucleotides as referring to hybridization probe rather than primer pair.

Q: But it's a matter of interpretation. You can't say that this language specifically excludes a shared primer pair, can you?

A: It doesn't specify it. It doesn't exclude it.

disclosure in Murakawa '450 that the "preselected site" should be chosen to avoid disrupting the primer binding sites (although it may be so chosen in a preferred embodiment). Hence, while Murakawa '450 original claims 18, 19 and 30 encompass use of a shared primer pair, they do not require or necessarily result in use of shared primer pair. It is possible to have a maxigene control sequence which can be amplified by different oligonucleotides and detected by the same oligonucleotides used for the target sequence. To find otherwise would be to limit claim terms to a preferred embodiment or inferences drawn from the description of a preferred embodiment. (See Bell Atlantic Network Services, supra. Cir. 1998). "The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency]." In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981) (quoting Hansgirg v. Kemmer, 102 F.2d 212, 214, 40 USPQ 665, 667 (CCPA 1939)). "Inherency ... may not be established by probabilities or possibilities." Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1268-69, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

Finally, Murakawa's argument (Paper 35, p. 22) that claim 30, when construed in light of claims 18 and 26 and the Murakawa '450 specification by one skilled in the art, requires a predetermined initial amount of a control sequence that binds the same primer pair as the target sequence is unpersuasive for the reasons given above, i.e., binding to a shared primer pair is neither excluded, required nor a necessary result.

Therefore, none of the earlier Murakawa claims, i.e., Murakawa claims filed or pending as of June 15, 1994 (Exs 1003, 2004-2008, 2021-2022 and 2024-2028), are directed to the same or substantially the same invention as claimed in the Wang 1993

patent because, although they recite use of a predetermined initial amount of a control sequence, none require or necessarily result in use of shared primer pairs.

VI. The earlier Murakawa claims cannot be analyzed as a group of related claims to the same invention

In its opposition (Paper 35, p. 15), Murakawa argues that "all of the Murakawa earlier claims that are drawn to substantially the same invention may be analyzed as a group to determine whether Murakawa has earlier claimed each and every one of the material limitations of the copied claims", citing Corbett for support.

In Corbett, the court held

> that there is a substantial difference between that which is to be gathered from the perusal of a group of related claims to the *same* invention and that which is to be gathered from the perusal of a group of claims to *related* inventions. The more divergent the subject matter of the individual claims, the less likely it is that the coverage of the interstices therebetween is realized.

Corbett, 568 F.2d at 766, 196 USPQ at 343-44 (original emphasis).

There is no dispute that Murakawa '959 claims 15-17 and 20 require a predetermined initial amount of a control sequence (FF 20). Murakawa still must show that one of the claims in Murakawa '959 contains a shared primer limitation in addition to the predetermined initial amount of control sequence limitation.

Murakawa contends that Murakawa '959 claim 9 uses the same language as Murakawa '450 claim 19, i.e., that the control sequence is "(iii) a sequence including said target and constructed by a multi-base insertion into a site in said viral RNA preselected with respect to said target sequence" (Paper 35, pp. 6-7) and that this language is supported by nearly identical disclosure in each of the Murakawa '959 and

'450 specifications (Paper 35, pp. 7-8).

37. Murakawa '959 claim 9 reads:

> A process as defined by claim 7
>
> [A process for minimizing false negative data in the identification of a target viral RNA sequence in a peripheral blood or H-9 cell sample which comprises
> (i) selecting said target viral RNA sequence;
> (ii) simultaneously subjecting (a) said sample and (b) at least one reference nucleotide which does not include said target sequence or which contains substantially more nucleotides than said target sequence;
> to polymerase chain reaction amplification under conditions appropriate to simultaneously amplify said target sequence if present in said sample and said reference sequence;
> (iii) denaturing the amplification products produced by step (ii);
> (iv) subjecting the denatured amplification products of step (iii) to hybridization conditions separately and sequentially with oligonucleotide probes homologous to said target sequence and to said reference sequence;
>
> whereby hybridization of the probe with the amplified reference sequence provides a positive control and minimizes the possibility of false negative data]
>
> in which said target viral sequence is located within the 3' ORF region of HIV-1 and in which the reference sequence utilized in step (ii) is located in the constant region of the beta chain of the T-cell receptor expressed [sic, in] T-cells affected by HIV-1.

First, we agree that Murakawa '959 claim 9 recites a control sequence which contains substantially more nucleotides than said target sequence, i.e., the constant region of the beta chain of the T-cell receptor. As discussed above, under the conditions of Murakawa '959 claim 9, a shared primer pair could not be used. Second, even assuming arguendo that Murakawa intended to rely on Murakawa '959 claim 7,

then Murakawa '959 claim 7, for the same reasons as given in regard to Murakawa '450 claim 19, includes, but does not require, a shared primer pair for the same reasons as given above. Third, we note the parallel between Murakawa '450 Examples I, VI and VII and Murakawa '959 Examples I, II and III (Ex. 2005, pp. 5-6). To wit, Murakawa '959 Example III is described as "Example I ... repeated with the exception that the maxigene primer is included in the reaction mixture" (Ex. 2005, p. 7).

Moreover, as noted by Wang in its reply (Paper 34, p. 10), "[a]ll other earlier Murakawa claims are directed to different, albeit related, inventions." A process for minimizing false negative data in the identification of a target viral RNA sequence is not directed to the same invention as the Murakawa claims in interference, i.e., a PCR-based method for determining the amount of a target nucleic acid sequence in a sample by simultaneously amplifying the target nucleic acid sequence and a known amount of an added control sequence with the same oligonucleotide primer pair in a single reaction mixture. In short, neither invention A (reciting only material limitation A) nor invention B (reciting only material limitation B) is the same invention as invention A+B (requiring both material limitations A and B). Thus, none of the earlier Murakawa claims relate to the same or substantially the same invention as claimed in the Wang 1993 patent because none of the Murakawa claims filed or pending as of June 15, 1994 require or necessarily result in both (A) a predetermined initial amount of a control sequence and (b) a shared primer pair.

VII. Conclusion

Accordingly, involved Murakawa '450 claims 34-35, 38-39 and 42-47 are barred

by 35 U.S.C. § 1.35(b)(1) by the Wang 1993 patent.

VIII. Limited remand to APJ

We remand this interference to the APJ to conduct any further proceedings, not inconsistent with this opinion, which may be necessary.

This panel decision is the law of the case. See 37 CFR § 1.640(c) with respect to any request for reconsideration of this decision.

RICHARD E. SCHAFER
Administrative Patent Judge

RICHARD TORCZON
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

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